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Inter-relationships between quinolinic acid, neuroactive kynurenines, neopterin and β_2-microglobulin in cerebrospinal fluid and serum of HIV-1-infected patients

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Summary

Quinolinic acid (QUIN) is an neurotoxic *N*-methyl-D-aspartate receptor agonist and an L-tryptophan metabolite of the kynurenine pathway. Increased concentrations of QUIN occur in both cerebrospinal fluid (CSF) and blood of patients infected with human immunodeficiency virus (HIV)-1, particularly those with neurologic disturbances. In the present study of HIV-1 infected patients in Walter Reed stages 4, 5 and 6, reductions in L-tryptophan accompanied proportional increases in L-kynurenine and QUIN in both serum and CSF. Further, close inter-correlations exist between QUIN kynurenic acid and L-kynurenine with both β_2-microglobulin and neopterin in CSF and serum. These correlations support the hypotheses that the kynurenine pathway is activated in association with inflammation and induction of indoleamine-2,3-dioxygenase. There were no relationships between CSF QUIN, L-kynurenine or kynurenic acid with the ratio of serum : CSF albumin concentrations, which indicates that the increases in CSF QUIN, L-kynurenine or kynurenic acid were not dependent on a breakdown of the blood–brain barrier. Kynurenic acid is also a kynurenine pathway metabolite that can attenuate the excitotoxic effects of QUIN when present in higher molar concentrations. While CSF kynurenic acid levels were increased in HIV-1-infected patients, the magnitude of the increases were smaller than those of QUIN and the molar concentrations of kynurenic acid were consistently lower than QUIN by at least one order of magnitude. We conclude that immune activation increases the levels of neuroactive kynurenines within the central nervous system of HIV-1-infected patients secondary to activation of indoleamine-2,3-dioxygenase.

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EXHIBIT B

(1)

Introduction

Substantially increased concentrations of the excitotoxin and kynurenine pathway metabolite, quinolinic acid (QUIN), are found in the cerebrospinal fluid (CSF) of patients infected with the human immunodeficiency virus (HIV-1; Heyes et al., 1989), particularly among patients with the AIDS dementia complex, aseptic meningitis or opportunistic central nervous system conditions (Heyes et al., 1991a). QUIN is an agonist of *N*-methyl-D-aspartate receptors and an excitotoxin. Notably, the concentrations achieved in the CSF of HIV-1-infected patients (Heyes et al., 1991a) exceeded levels reported to be neurotoxic in vitro (Giulian et al., 1990; Whetsell and Schwarcz, 1989). Consequently, we have postulated that QUIN may be involved in the neurologic complications of HIV-1 infection, including the AIDS dementia complex (Heyes et al., 1989, 1991a). The potential role of *N*-methyl-D-aspartate receptors in mediating neuronal damage in HIV-1-infection has been further highlighted by subsequent in vitro studies (Giulian et al., 1990; Lipton et al., 1991).

Other factors, however, may influence the neurologic effects of QUIN and other *N*-methyl-D-aspartate receptor agonists. In particular, the related kynurenine pathway metabolite kynurenic acid (KYNA) can attenuate the excitotoxic effects of QUIN by virtue of its antagonist effects on excitatory amino acid receptors, including *N*-methyl-D-aspartate receptors (Foster et al., 1984). Therefore, the balance between the concentrations of QUIN and KYNA may influence whether the excitotoxic effects of QUIN or other neurotoxins are manifest. The present study sought to determine whether the levels of KYNA are in-

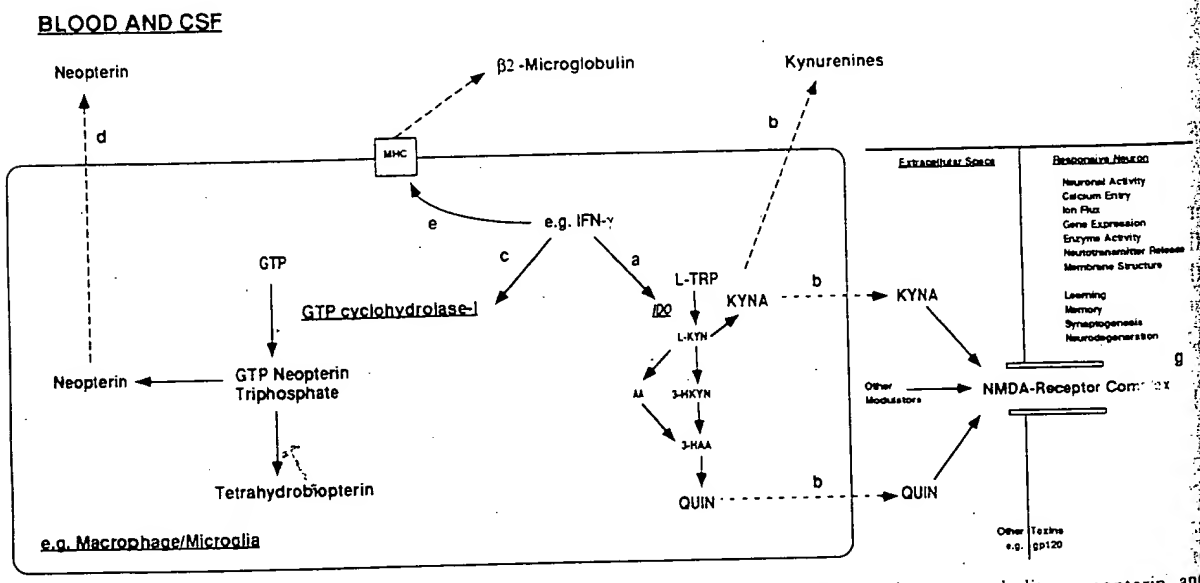

Fig. 1. Model of the metabolic relationships between selected cytokines, kynurenine pathway metabolites, neopterin and β_2-microglobulin and the potential role of *N*-methyl-D-aspartate (NMDA) in neuronal dysfunction and neurodegeneration in HIV-1 infection and other inflammatory diseases. Broken lines represent transfer of substrate from one metabolic compartment to another, solid lines represents metabolic reactions or effects of agents on enzymes or receptors. Enzymes are underlined. Interferon-γ (IFN-γ) and other cytokines increase indoleamine-2,3-dioxygenase (IDO) activity in macrophages and other cells (a) and increase the conversion of L-tryptophan to L-kynurenine (L-KYN), KYNA, anthranilic acid (AA), 3-hydroxykynurenine (3-HKYN), 3-hydroxyanthranilic acid (3-HAA) and QUIN which may enter the blood, CSF and extracellular fluid space of the brain (b). IFN-γ also activates guanosine triphosphate (GTP) cyclohydrolase-I and increases the synthesis of neopterin (c) which also appears in the blood and CSF (d). The release of β_2-microglobulin is also increased by IFN-γ (e). Increased concentrations of QUIN, kynurenic acid and other modulators of *N*-methyl-D-aspartate receptor activity may induce neuronal dysfunction and nerve cell death and thereby result in neurologic symptoms (g). Strategies to alter the synthesis of *N*-methyl-D-aspartate receptor ligands or attenuate their effects offer new approaches to therapy in inflammatory diseases.

creased in the CSF, and investigate the relationship of KYNA to QUIN and other neuroactive kynurenines in the CSF of HIV-1-infected patients.

The increases in CSF and serum QUIN in HIV-infected patients have been attributed to induction of indoleamine-2,3-dioxygenase, the first enzyme of the kynurenine pathway which converts L-tryptophan to L-kynurenine (Fig. 1). The increases in both brain and lung indoleamine-2,3-dioxygenase activity in non-human primate models of AIDS are consistent with this hypothesis (Saito et al., 1991a). To further investigate the role of indoleamine-2,3-dioxygenase in changing kynurenine pathway metabolism, we used the concentrations of L-tryptophan and L-kynurenine in blood and CSF as an index of indoleamine-2,3-dioxygenase activity (Fuchs et al., 1990; Heyes and Lackner, 1990; Saito et al., 1991a) and determined their relationships to QUIN and KYNA. In addition, because host immune mediators such as interferon-γ and tumor necrosis factor-α may increase indoleamine-2,3-dioxygenase activity, QUIN production, neopterin synthesis, and β_2-microglobulin expression (Pfefferkorn and Guyre, 1984; Byrne et al., 1986; Bianchi et al., 1988; Saito et al., 1991b; Heyes et al., 1991, 1992a, b), we examined the relationship of kynurenine pathway metabolites with neopterin and β_2-microglobulin, which are 'markers' of immune stimulation (see Fig. 1). The potential role of disruption of the blood–brain barrier was studied by measuring the CSF : serum albumin ratio.

Materials and methods

Subjects studied

Samples of both CSF and serum were collected from HIV-1-infected patients who were being studied at the Memorial Sloan-Kettering Cancer Center. Blood was collected from an arm vein and serum was isolated by centrifugation. CSF was collected from the lumbar sac. The clinical characteristics of these patients have been described previously (Brew et al., 1989, 1990; Heyes et al., 1991a). The systemic disease state of these subjects was classified according to the Walter Reed (WR) Staging system (WR 4-5, n = 40; WR 6, n = 39 (Redfield et al., 1986). AIDS dementia complex scores (0–4) were determined according to published criteria (Brew et al., 1989). The number of patients in each group were: demented, WR 4-5, n = 20; WR 6, n = 28; or not demented, WR 4-5, n = 20; WR 6, n = 11. Patients were studied in various stages of systemic and central nervous system disease. None of the patients had clinical aseptic meningitis (Hollander and Stringari, 1987), demonstrable opportunistic central nervous system infections or neoplasms. Because the samples were obtained before the approval or widespread use of zudovudine (azidothymidine or AZT), none of the patients were receiving anti-retroviral therapies at the time of sample collection. Control subjects were 22 age-matched healthy and neurologically unimpaired volunteers.

Biochemical measurements

Samples were assayed by experienced laboratory personnel, using established and verified methods, without prior knowledge to the patients' viral or clinical status. QUIN was quantified by electron capture negative chemical ionization gas chromatography/mass spectrometry which uses [^{18}O]QUIN as internal standard, rather than structural isomers or chemical analogs (Heyes and Markey, 1988). The concentrations of KYNA, L-kynurenine and L-tryptophan in CSF and serum were quantified by high performance liquid chromatography with either fluorescence detection (Heyes and Quearry, 1990) or ultraviolet light absorbance spectrometry (adapted from Holmes, 1988) or electrochemical detection (Heyes and Markey, 1988) respectively. Generally, measures were made within the same assay run. However, where more than one assay run was done, selected samples from previous assays were included in subsequent procedures to ensure replicate values were within established and acceptable variability limits. In no case could group mean differences be attributed to systematic assay errors. In other studies, no gradients for QUIN, KYNA or L-kynurenine have been noted along the CSF axis (Mouradian et al., 1989; Heyes and Sunderland, unpublished observations). β_2-Microglobulin and neopterin were mea-

sured in CSF and serum by radioimmunoassay (Electronuclonics-Diagnostics. Piscataway NJ. and Henning, Berlin, respectively). The integrity of the blood–brain barrier was assessed by measuring the ratio of CSF : serum albumin concentrations (Brew et al., 1989). Measures of albumin, IgG and white blood cell counts were done by routine laboratory methods.

Statistical analyses

Results were analysed by one-way analysis of variance with Dunnett's *t*-test for multiple comparisons (Feldman et al., 1987). All regression analyses were done using the method of least squares after logarithmic transformation (Table 1). Non-parametric correlation coefficients were calculated as the Spearman Rank Correlation coefficient. Values presented are mean ± one standard error of the mean or percent of control subjects unless otherwise stated.

Results

Relationships between L-kynurenine, L-tryptophan, KYNA and QUIN

The concentrations of CSF L-tryptophan, L-kynurenine, KYNA and QUIN concentrations as well as the ratio of QUIN : KYNA in HIV-1-infected patients are presented in Fig. 2. Systemic disease was classified as WR 4-5 or WR 6 (AIDS) and neurologic disease was classified as either not demented (AIDS dementia complex scores ≤ 0.5) or demented (AIDS dementia complex scores ≥ 1). Values are expressed as a percent of age-matched control subjects and plotted on a logarithmic scale. The increases in L-kynurenine, KYNA and QUIN were largest in both groups of demented patients compared to same stage non-demented patients. The increases in CSF QUIN in demented patients was approximately the same in the WR 4-5 patients as in the WR 6 patients. However, the highest ratio of QUIN : KYNA in the CSF was found in the demented WR 6 patients. In the HIV-1-infected patients taken collectively, there were significant inter-correlations between the concentrations of L-kynurenine, KYNA, QUIN, neopterin, β_2-microglobulin and IgG in the CSF (Table 1). In contrast, among the WR 4–6 patients, there was an inverse correlation between CSF L-tryptophan with CSF QUIN, KYNA and L-kynurenine (Table 1).

There were no significant differences in serum QUIN, L-kynurenine or L-tryptophan between the four sub-groups of HIV-1-infected patients and the data were pooled for comparison to control subjects. The percent changes in the serum parameters were substantially less than the percent changes in the CSF. Serum L-kynurenine concentrations were increased in the WR 4–6 patients (4.14 ± 0.25 μM, $n = 44$) compared to controls

TABLE 1

CORRELATION COEFFICIENTS BETWEEN QUIN, KYNA, L-KYN, L-TRP, NEOPTERIN AND β_2-MICROGLOBULIN IN HIV-1-INFECTED PATIENTS

	Correlation coefficient (r)	P-value
CSF		
log QUIN vs. log KYNA	+0.86	$P < 0.0001$
log QUIN vs. log L-kynurenine	+0.76	$P < 0.0001$
log QUIN vs. L-tryptophan	−0.40	$P < 0.005$
log QUIN vs. log neopterin	+0.71	$P < 0.0001$
log QUIN vs. log β_2-microglobulin	+0.69	$P < 0.0001$
log QUIN vs. log IgG	+0.46	$P < .005$
log KYNA vs. log L-kynurenine	+0.85	$P < 0.0001$
log KYNA vs. L-tryptophan	−0.50	$P < 0.01$
log KYNA vs. log neopterin	+0.79	$P < 0.0001$
log KYNA vs. log β_2-microglobulin	+0.74	$P < 0.0001$
log KYNA vs. log IgG	+0.80	$P < 0.002$
log L-kynurenine vs. L-tryptophan	−0.41	$P < 0.02$
log L-kynurenine vs. log neopterin	+0.56	$P < 0.005$
log L-kynurenine vs. log β_2-microglobulin	+0.58	$P < 0.0001$
log L-kynurenine vs. log IgG	0.34	$P < .05$
Serum		
log QUIN vs. log L-kynurenine	+0.75	$P < 0.0001$
log QUIN vs. L-tryptophan	−0.31	$P < 0.02$
log QUIN vs. log neopterin	+0.70	$P < 0.0001$
log QUIN vs. log β_2-microglobulin	+0.68	$P < 0.0001$
L-KYN vs. L-tryptophan	−0.32	$P < 0.01$
L-KYN vs. log neopterin	+0.69	$P < 0.0001$
L-KYN vs. log β_2-microglobulin	+0.54	$P < 0.0002$
L-Tryptophan vs. log neopterin	−0.43	$P < 0.001$
L-Tryptophan vs. log β_2-microglobulin	−0.36	$P < .02$

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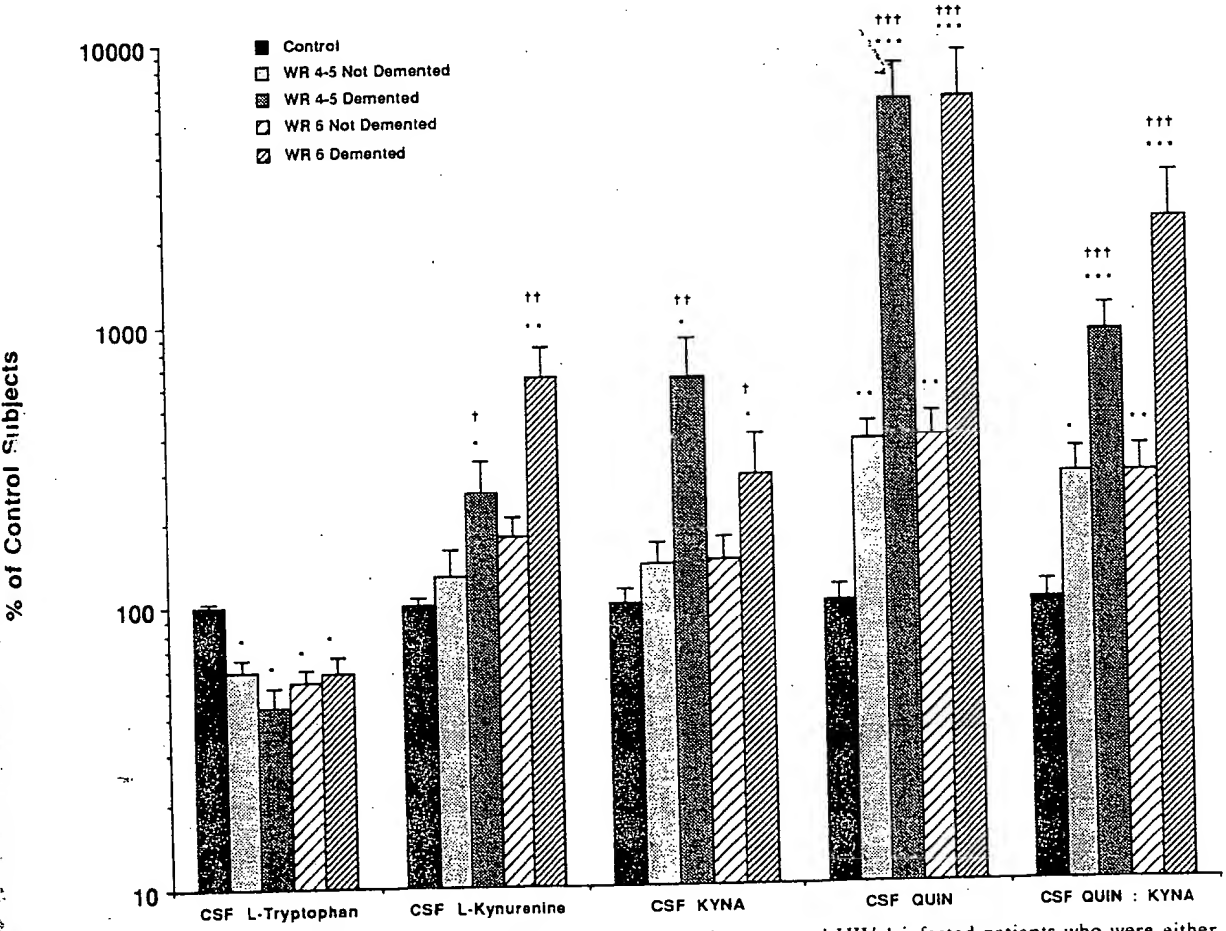

Fig. 2. CSF L-tryptophan, L-kynurenine, KYNA and QUIN concentrations in untreated HIV-1-infected patients who were either demented (WR 4-5, $n = 20$; WR 6, $n = 28$) or not demented (WR 4-5, $n = 20$; WR 6, $n = 11$). No patients had opportunistic CNS conditions, aseptic meningitis or were being treated with anti-retroviral drugs). Values presented are expressed as a percent of age-matched neurologically normal volunteers (L-tryptophan, 2.32 ± 0.09 μM; L-kynurenine, 52.9 ± 3.1 nM; KYNA, 3.49 ± 0.44 nM and QUIN 22.0 ± 3.3 nM). * $P < 0.05$, ** $P < 0.001$, *** $P < 0.005$, **** $P < 0.0001$ versus control; † $P < 0.05$, †† $P < 0.005$, ††† $P < 0.0001$ versus respective not demented WR stage. Note: there are no gender differences, and no gradients for QUIN, KYNA, L-kynurenine or L-tryptophan along the CSF axis. Furthermore, brain atrophy, neurodegeneration, dementia or motor disturbances cannot account for these increases as CSF L-tryptophan, L-kynurenine, KYNA and QUIN concentrations are either normal or reduced in patients with either Huntington's disease, Alzheimer's disease, complex partial seizures, bipolar and unipolar depression, bulimia nervosa, anorexia nervosa or schizophrenia (Heyes et al., Brain, in press).

between CSF and serum L-kynurenine concentrations ($r = 0.65$, $P < 0.0001$).

Relationships of kynurenine pathway metabolites to AIDS dementia complex scores

As well as the significant correlations between CSF QUIN, neopterin and β_2-microglobulin with AIDS dementia complex scores noted previously (Brew et al., 1989, 1990; Heyes et al., 1991a), significant correlations between CSF L-kynurenine ($P < 0.002$) and the CSF QUIN : KYNA ratio ($P < 0.05$) with AIDS dementia complex scores were also noted.

Relationships of kynurenine pathway metabolites to neopterin, β_2-microglobulin and blood–brain barrier integrity

The inter-relationships between QUIN, KYNA and L-kynurenine with both neopterin, β_2-microglobulin and IgG are summarized in Table 1, and support a link between kynurenine pathway metabolism and immune stimulation within both the brain and periphery (Fig. 1). In CSF and serum, both neopterin and β_2-microglobulin concentrations were higher in the WR 4–6 patients compared to controls (see Brew et al., 1989, 1990). In the WR 4–6 patients, there were significant correlations between concentrations of neopterin, β_2-microglobulin and concentrations of CSF IgG with QUIN, KYNA and L-kynurenine.

There were no significant differences in the CSF : serum albumin ratio in the four groups of HIV-1-infected patients. There were also no significant correlations between CSF : serum albumin ratio with CSF QUIN, KYNA, L-kynurenine or L-tryptophan, except the modest correlation with CSF QUIN noted only in demented patients taken collectively (see Heyes et al., 1991a). CSF white blood cell counts were < 10 cells/ml in 93% of samples studied and there were no correlations between CSF QUIN, KYNA, L-kynurenine or L-tryptophan with CSF white blood cell counts.

Serum QUIN and L-kynurenine levels were significantly correlated with both serum β_2-microglobulin and neopterin in the WR 4–6 patients. Conversely, serum L-tryptophan levels were inversely correlated with serum QUIN, L-kynurenine, β_2-microglobulin and neopterin concentrations.

Discussion

QUIN and other putative activators of *N*-methyl-D-aspartate receptors have been implicated in the etiology of HIV-1 neurologic disease (Heyes et al., 1988, 1989, 1991a; Giulian et al., 1990; Lipton et al., 1991). Importantly, QUIN has also been proposed as a neurotoxin in other inflammatory neurologic diseases, because of the sensitivity of indoleamine-2,3-dioxygenase to activation by endotoxin and interferon-γ, and because substantial increases in CSF QUIN concentrations are found in patients with inflammatory neurologic disease (Takikawa et al., 1986, 1988; Heyes et al., 1988; Heyes and Lackner, 1990; Saito et al., 1991b; Halperin and Heyes, 1992). The purpose of the present study was to determine whether the CSF levels of KYNA, a modulator of QUIN neurotoxicity, are also increased in HIV-1-infected patients. We also investigated potential mechanisms that may be involved in increasing QUIN synthesis. The results demonstrate that the substantial increases in CSF QUIN levels in HIV-1-infected patients are accompanied by parallel increases in KYNA. The results strongly support activation of indoleamine-2,3-dioxygenase in direct proportion to the degree of intrathecal immune activation.

Studies in experimental animals have shown that KYNA can protect neurons against the excitotoxic effects of QUIN. However, a ratio of up to 3 : 1 in favor of KYNA is needed for maximal protection (Boegman et al., 1990; Foster et al., 1984). While it is not known whether this relationship between QUIN, KYNA and excitotoxicity applies to humans, it is of note that the ratio of QUIN : KYNA actually favors QUIN in normal subjects (8.71) and is further increased in the HIV-1 infected patients (Fig. 2). Analogous increases in the ratio of QUIN : KYNA have also been noted in primate models of AIDS and septicemia (Heyes et al., 1990a, b, 1992; Heyes and Lackner, 1990). Therefore, the ratio of QUIN : KYNA favours QUIN excitotoxicity. Also, while increases in brain KYNA levels may be viewed as potentially beneficial in attenuating the excitotoxic effects of QUIN and other excitotoxins, it is possible that KYNA as an antagonist of excitatory amino acid neurotransmitters may con-

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tribute to the neurologic deficits by blocking excitatory amino acid receptors during immune activation. QUIN may also interfere with excitatory neurotransmission and thereby produce neurologic deficits by a non-cytolytic mechanism.

A model of possible mechanisms for increases in CSF and serum QUIN in HIV-1 infection, as well as other conditions of immune activation, also applies to the increases in CSF KYNA and L-kynurenine (Fig. 1; Takikawa et al., 1986; Heyes et al., 1990a, 1991a; Heyes and Lackner, 1990). KYNA may be derived from L-kynurenine that had been taken up either by the brain from the blood (Gal and Sherman, 1980; Heyes and Quearry, 1990), or synthesized within the brain (Heyes and Quearry, 1990) secondary to activation of indoleamine-2,3-dioxygenase. The increases in the activity of indoleamine-2,3-dioxygenase in both lung and brain of macaques infected with the Simian immunodeficiency virus or the type-D retrovirus are consistent with both systemic and central synthesis (Heyes et al., 1990b; Saito et al., 1991a). The inverse correlations in the present study between L-tryptophan with both QUIN and L-kynurenine in the CSF of HIV-1-infected patients, but not in the CSF of control subjects, is in accordance with increased brain indoleamine-2,3-dioxygenase activity (Table 1). Further, the positive correlations between CSF levels of L-KYN, KYNA and QUIN support increased substrate flux through the kynurenine pathway within the CNS (Table 1). It is of note that the magnitude of the increases in CSF L-kynurenine and QUIN are substantially greater than the increases in serum. This phenomenon has been noted in other inflammatory disease conditions (Halperin and Heyes, 1992; Heyes and Lackner, 1990; Heyes et al., 1990a, b, 1992a). Nevertheless, substrates derived from blood may be important sources of L-kynurenine, KYNA and QUIN, particularly if the levels of systemic immune activation is marked, for example during septicemia (Heyes and Lackner, 1990).

The model (Fig. 1) proposes that macrophages are a principle source for QUIN (Heyes et al., 1991a). Infiltrates of macrophages and reactive microglia are a well-established neuropathologic feature of HIV-1 infection, and are also found in many other conditions of CNS inflammation. Macrophages convert [$^{13}C_6$]-L-tryptophan to [$^{13}C_6$]-QUIN, particularly when stimulated with interferon-γ, and the concentrations achieved in the incubation medium (24 μm) exceed those noted in the CSF of HIV-1-infected patients (up to 15 μM; Heyes et al., 1992b; Brew and Heyes, unpublished observations). This observation demonstrates that macrophages contain the enzymes necessary to convert L-tryptophan to QUIN. Consequently, it is likely that the activity of other enzymes of the kynurenine pathway are also increased following intracerebral immune activation and macrophage infiltration. Other cells may also convert precursors to QUIN, including astrocytes, which contain 3-hydroxyanthranilate-3,4-dioxygenase (Okuno et al., 1987). The accumulation of QUIN may also reflect the relatively low activity of quinolinic acid phosphoribosyltransferase, the degradation enzyme for QUIN (Foster et al., 1985).

Both indoleamine-2,3-dioxygenase and GTP cyclohydrolase I activity are increased by interferon-γ, tumor necrosis factor-α and other cytokines in macrophages and other cell types (Fig. 1; Niederwieser et al., 1986; Bianchi et al., 1988; Fuchs et al., 1988; Heyes et al., 1992b). Therefore, strong inter-correlations between QUIN, KYNA, L-tryptophan and L-kynurenine with neopterin, β_2-microglobulin and IgG concentrations in the CSF support a link between indoleamine-2,3-dioxygenase induction with intrathecal inflammatory responses (Table 1; Fuchs et al., 1990; Heyes et al., 1991b, 1992a). These correlations also suggest increased interferon-γ activity within the central nervous system (Griffin et al., 1991). There was minimal evidence that the group increases in CSF QUIN, KYNA or L-kynurenine could be attributed to disruption of the blood–brain barrier. Similar conclusions have been drawn regarding the source of elevated neopterin and β_2-microglobulin in CSF (Brew et al., 1989,1990; Griffin et al., 1991).

Dietary L-tryptophan intake was not regulated or quantified in the present study and we cannot exclude the possibility that at least some of the reductions in serum and CSF L-tryptophan concentrations were diet-dependent. However, reduced L-tryptophan intake would be expected to either decrease not only L-tryptophan levels but

also L-kynurenine, KYNA and QUIN concentrations. The reductions in CSF L-tryptophan levels were independent of blood L-tryptophan concentrations, and indicate that the central and systemic L-tryptophan compartments are influenced separately, such as by different local indoleamine-2,3-dioxygenase activities in central nervous system and systemic tissues. The uptake of L-tryptophan into the brain may have also been influenced by changes in the concentrations of large neutral amino acids in the blood of HIV-1-infected patients (Fernstrom, 1983). The levels of large neutral amino acids are reduced in some HIV-1-infected patients (Althoff et al., 1989), which would promote L-tryptophan entry into the CNS (Fernstrom, 1983). Therefore, these observation argue in favor of a role for indoleamine-2,3-dioxygenase induction in accelerating the conversion of L-tryptophan to L-kynurenine, KYNA and QUIN. Depletion of L-tryptophan may reduce the synthesis of serotonin and other indoleamines (Larsson et al., 1989; Heyes et al., 1990a), as well as interfere with the metabolism of protein in both systemic and central nervous system tissues.

While it is clear that induction of indoleamine-2,3-dioxygenase, the depletion of L-tryptophan and increased substrate flux through the kynurenine pathway are associated with immune activation, the reason for this response remains to be established. The magnitude of the increases in kynurenine pathway metabolism, particularly within the central nervous system, and the widespread circumstances in which it occurs, indicate that the reasons and consequences are not trivial. There are arguments that such responses may be both beneficial as well as detrimental. On the positive side, studies in vitro have suggested that activation of indoleamine-2,3-dioxygenase and depletion of intracellular L-tryptophan may be one mechanism by which interferon-γ exerts anti-microbial and anti-proliferative effects on some intracellular parasites and tumor cells (Pfefferkorn and Guyre, 1984; Byrne et al., 1986; Takikawa et al., 1988), but not on others (Turco and Winkler, 1986; Takikawa et al., 1988). Also, the reactions catalysed by indoleamine-2,3-dioxygenase metabolize potentially toxic oxygen-free radicals (Daley-Yates et al., 1988; Siesjo et al., 1989; Sono, 1989). Conversely, depletion of L-tryptophan may impair protein synthesis and indoleamine metabolism. The production of potentially neurotoxic kynurenine pathway metabolites, including QUIN, L-kynurenine and KYNA, may be another detrimental consequence of indoleamine-2,3-dioxygenase induction. At this point in time, it is not possible to state where the balance between beneficial versus detrimental consequences lies.

Indoleamine-2,3-dioxygenase induction and production of kynurenine pathway metabolites occur in a wide spectrum of immune stimulation (Pfefferkorn and Guyre, 1984; Byrne et al., 1986; Takikawa et al., 1986; Werner et al., 1987, 1989; Bianchi et al., 1988; Heyes and Lackner, 1990; Heyes et al., 1988, 1990b, 1992; Saito et al., 1991a, b). In view of the neuroactive nature of kynurenine pathway metabolites, we propose that such compounds may be final common mediators of neuronal dysfunction and death in inflammatory neurologic disease. This disruption would include functions mediated via *N*-methyl-D-aspartate receptors, such as learning, memory and synaptic plasticity (Morris et al., 1987). Therefore, strategies to attenuate the neurotoxic effects of QUIN (without disrupting *N*-methyl-D-aspartate receptor function), or reducing the synthesis of neuroactive kynurenine pathway metabolites, may offer new approaches to therapy of the neurologic deficits associated with HIV-1 infection. Notably, such strategies may also be of benefit in other inflammatory neurologic diseases.

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Summary

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